Gold versus Palladium: A Regioselective Cycloisomerization of Aromatic Enynes

Jessy Aziz, Gilles Frison, Patrick Le Menez, Jean-Daniel Brion, Abdallah Hamze, Mouad Alami

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

Gold *versus* Palladium: A Regioselective Cycloisomerization of Aromatic Enynes

Jessy Aziz,[a] Gilles Frison,[b] Patrick Le Menez,[a] Jean-Daniel Brion,[a] Abdallah Hamze,[a,]* and Mouad Alami[a,]*

[a] Univ Paris-Sud, CNRS, BioCIS - UMR 8076, LabEx LERMIT, Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, 5 rue J.-B. Clément, Châtenay-Malabry, F-92296, France

[b] Laboratoire des Mécanismes Réactionnels, Department of Chemistry, Ecole polytechnique and CNRS, 91128 Palaiseau Cedex, France

Fax: (+33)-1-46835828; phone: (+33)-1-46835498; e-mail: abdallah.hamze@u-psud.fr or mouad.alami@u-psud.fr

Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201

Aromatic enynes can be transformed into arylnaphthalenes or benzofulvenes depending on the reaction conditions. Under gold(I) catalysis, exclusive or major 6-*endo-dig* cyclization took place leading to arylnaphthalenes. However, a catalytic system based on palladium iodide/1,3-Bis(diphenylphosphino)propane, in the presence of cesium carbonate as a base was necessary to furnish exclusively 5-*exo-dig* cyclization pattern, regardless to the electronic effects of the substituents. In the latter transformation, a mechanistic study (Kinetic Isotopic Effect, Density Functional Theory) involving a C-H activation is suggested for the exclusive benzofulvenes formation.

Keywords: aromatic enynes; cycloisomerization; regioselectivity; gold; palladium

Introduction

In the past few decades, myriads of transition metal-catalyzed carbon-carbon cross-coupling reactions have been discovered and developed.[1] Among the extraordinary variety of the transformations reported, 1,n-enynes cycloisomerizations are growing in importance as the most valuable strategies for the synthesis of functionalized cyclic structures.[2] The significance of this process stems in part from the rapid increase in structural complexity, starting with relatively simple acyclic subunits containing ene and yne fragments,[3] and secondly, this procedure is inherently atom economic. In addition to that, intra- or intermolecular addition reactions to alkynes became broadly explored due to the recent significant advances in the development of transition metal complexes capable of catalyzing enyne cycloisomerizations, such as Ag(I),[4] Au(I),[5] Au(III),[6] Pd(II),[7] Pt(II),[2, 8] Rh(III),[9] Ru(II),[10] and W(0).[11]

Gold-catalyzed cycloisomerization of enyne compounds leading to carbocycles and heterocycles has been actively investigated.[12] Recently, Fürstner and co-workers synthesized phenanthrenes by a transition-metal π-activation of *ortho*-alkynylated biaryl derivatives via a 6-*endo-dig* cyclization (Figure 1, equation 1).[8b] However, the reaction took place only in the presence of electron-donating groups, which seems to be important for the 6-*endo-dig* cyclization process. The presence of strongly electron

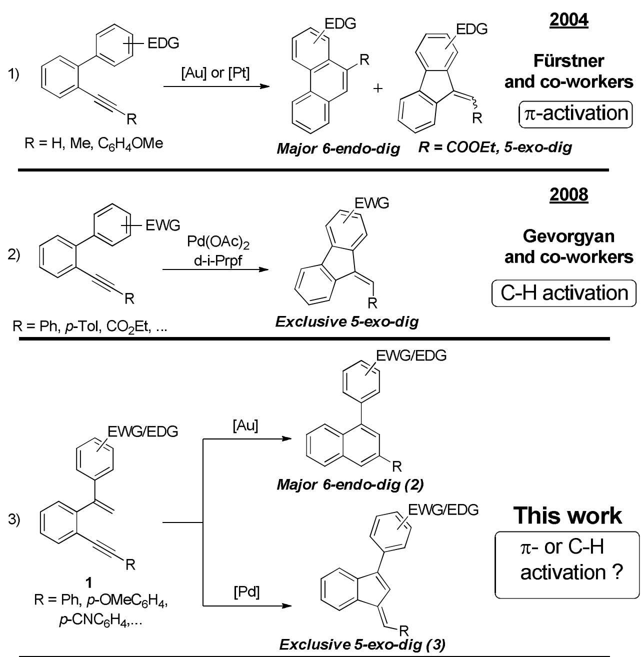


Figure 1. Intramolecular cycloisomerization of 1,5-enynes.

withdrawing ester group on the alkyne not only diminishes the reaction rate but also overturns this inherent bias furnishing a 5-*exo-dig* ring closure fluorene derivative. Two years later, Shibata and co-workers[5a] reported a gold-catalyzed cycloisomerization of aromatic enynes giving mainly the 6-*endo-dig* ring closure products. The scope of this method was limited to alkyl substituents or neutral phenyl group. In 2008, Gevorgyan's team[7b,

[13] described an exclusive regio- and stereoselective formation of 9-benzylidene-9*H*-fluorene derivatives catalyzed by $Pd(OAc)_2$ and a ferrocene-type ligand (Figure 1, equation 2). A C–H activation mechanism was proposed, in opposition to the most common electrophilic activation process. In this case also, the electronic effect of the substituents played a major role, since very good yields were obtained with substrates having electron-withdrawing groups and a drop in the reaction yields was observed with those bearing electron-donating groups.

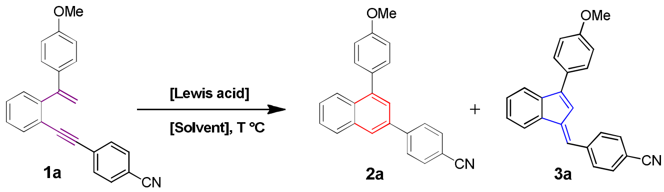
From the above observations, a complete control of the regioselectivity of the intramolecular ring closure of aromatic enynes is still a challenge given that it depends on several parameters: nature of the catalyst, electronic effects of the substituents and mechanism of the reaction.

In this paper, we wish to disclose our findings on the cycloisomerization of aromatic enynes **1** (Figure 1, equation 3). We were able to obtain under Au(I) catalysis mainly phenylnaphthalene derivatives **2** *via* a 6-*endo-dig* cyclization, and under Pd(II) catalysis benzofulvene derivatives **3** *via* an exclusive 5-*exo-dig* cyclization, regardless to the electronic effects of the substituents. The mechanism of the Pd catalyzed cycloisomerization of enynes **1** was studied to determine if the reaction evolves either by π or by C-H activation.

Results and Discussion

We began our investigations by testing the reactivity of enyne **1a** in the presence of Au(I) or Au(III) catalysts (Table 1).[14] Treatment of **1a** with $AuCl_3$/AgOTf (5 mol %) in THF at 70 °C gave phenylnaphthalene **2a** in a 74% yield, together with a low amount of benzofulvene **3a** (9%, Table 1, entry 1). Switching from $AuCl_3$ to $(PPh_3)AuCl$ resulted in a slight increase of the yield of **2a** (entry 2). When $(PPh_3)AuCl$ complex or AgOTf were used alone, they were unable to promote the intramolecular ring closure, and the starting material **1a** was fully recovered (entries 3 and 4). We were delighted to find that the use of a silver-free salt complex $Ph_3PAuNTf_2$[15] (5 mol %) in THF gave the best result (entry 5). Changing the solvent sources (CH_2Cl_2, toluene, 1,4-dioxane) did not affect the reaction outcome. In agreement with the results obtained by Fürstner,[8b] $PtCl_2$ and $InCl_3$ salts also catalyze the intramolecular cyclization of **1a**, providing the expected substituted naphthalene **2a** in a 76% and 85% yield, respectively. A control experiment revealed that by heating enyne **1a** in THF at 70 °C for 12 h in the absence of any catalyst (entry 8) no ring closure product was observed, clearly suggesting that the cycloisomerization reaction is not just a thermal electrocyclization process but definitely requires assistance by a soft Lewis acid. The whole set of experiments (entries 1-7) showed a pronounced preference for the 6-*endo-dig* cyclization giving **2a**

Table 1. Lewis acids effect on the hydroarylation of the enyne **1a**.[a]

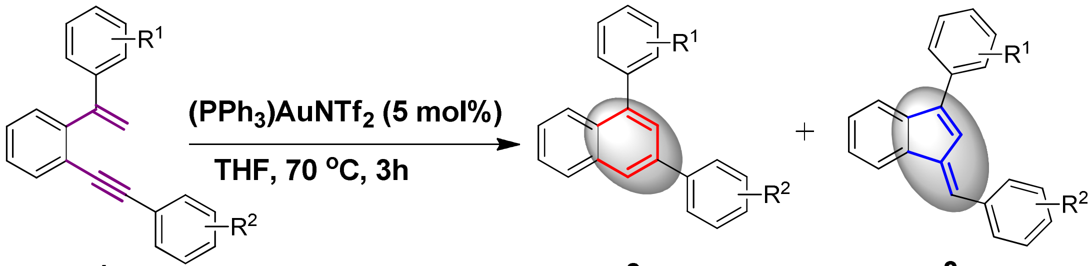


Entry	Catalyst	Ligand	Base	Yields[b] 2a	3a
1	$AuCl_3$/AgOTf	-	-	74	9
2	$(PPh_3)AuCl$/AgOTf	-	-	88	10
3[c]	$(PPh_3)AuCl$	-	-	0	0
4[c]	AgOTf	-	-	0	0
5	**$(PPh_3)AuNTf_2$**	-	-	**90**	**7**
6[d]	$PtCl_2$	-	-	76	11
7[d]	$InCl_3$	-	-	85	10
8[c]	-	-	-	0	0
9[c],[e]	$PdCl_2(MeCN)_2$	-	-	-	-
10	$PdCl_2(MeCN)_2$	dppp	Cs_2CO_3	-	66
11	$PdCl_2(MeCN)_2$	dppp	K_2CO_3	-	43
12	$PdCl_2(MeCN)_2$	dppp	NaO*t*Bu	-	14
13	$Pd(OAc)_2$	dppp	Cs_2CO_3	-	55
14[f]	**PdI_2**	**dppp**	**Cs_2CO_3**	-	**77**
15	PdI_2	dppe	Cs_2CO_3	-	68
16	PdI_2	dppf	Cs_2CO_3	-	20
17[g]	$Pd(OAc)_2$	D-*i*-Prpf	-	6	27
18	PdI_2	D-*i*-Prpf	Cs_2CO_3	10	8
19	PdI_2	XPhos	Cs_2CO_3	-	8

[a] Unless otherwise noted, Reaction conditions are: **Entries 1-8:** Enyne **1a** (0.6 mmol), catalyst (5 mol%), AgOTf when used (5 mol%), THF (1 mL) at 70 °C for 3 h under argon. **Entries 9-19:** Enyne **1a** (0.6 mmol), Pd (10 mol%), ligand (20 mol%), base (1 eq), 1,4-dioxane (2 mL) in a sealed tube at 150 °C for 15 h.
[b] Yield of isolated product.
[c] **1a** was completely recovered.
[d] Reaction conducted in toluene at 90 °C.
[e] Reaction's time = 6 h.
[f] **1a** was completely recovered when the reaction was conducted without ligand and/or base.
[g] Reaction was conducted in toluene at 120 °C for 3 h, a mixture of *E*- and *Z*-isomers of **3a** was obtained in 70/30 *E/Z* ratio.

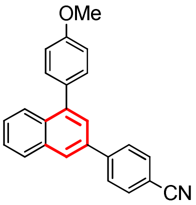
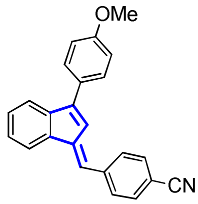
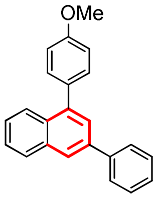
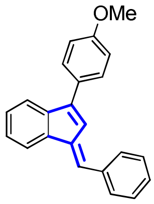
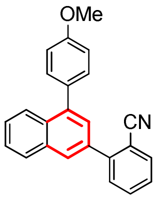
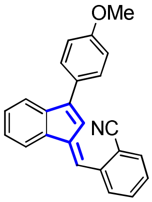
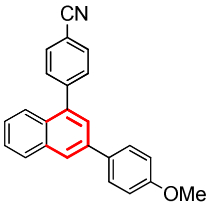
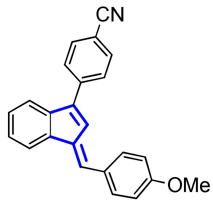
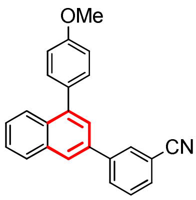
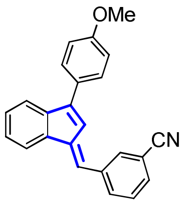
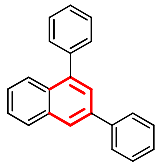
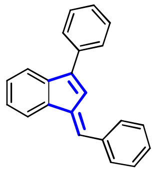
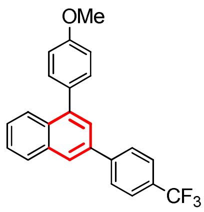
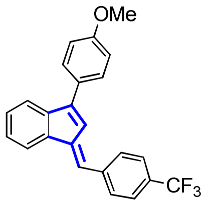
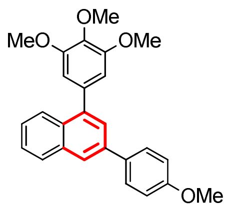
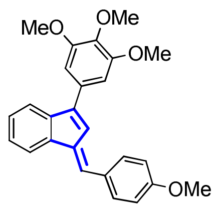
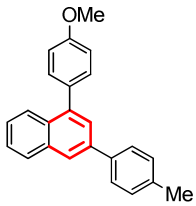
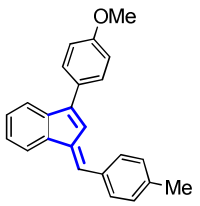
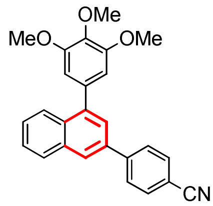
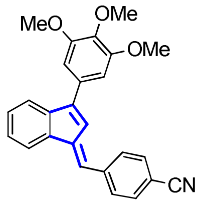
over the conceivable 5-*exo-dig* mode. Not more than 12% of benzofulvene **3a** were formed.
In continuation of this study, we investigated whether **3a** could be exclusively formed, reversing the regio-selectivity observed with gold, platinum or indium catalysts. For these reasons, we turned our attention to the use of palladium complexes (Table 1, entries 9-19).
First, when $PdCl_2(MeCN)_2$ was employed at 150 °C for 6 h, no reaction occurred and **1a** was completely recovered (Table 1, entry 9).[14] After several assays, we determined that the addition of 1,3-bis(diphenylphosphino)propane (dppp) as a ligand, under basic conditions (Cs_2CO_3) and heating at 150 °C for 15 h afforded exclusively **3a** in a 66% yield (entry 10). Optimization assays with respect to the base revealed that Cs_2CO_3 is the best base (entries 10-12). Among other palladium sources examined (entries 10, 13 and 14), PdI_2 proved to be the catalyst of choice, providing exclusively the 5-*exo-dig*

Table 2. Intramolecular cycloisomerization of aromatic enynes **1** under Au-catalysis.



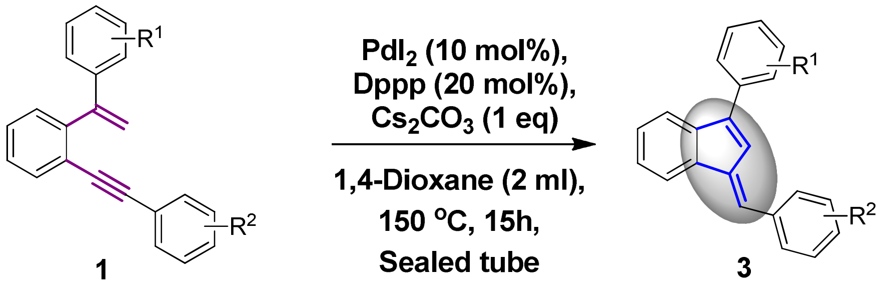
1 **2** **3**

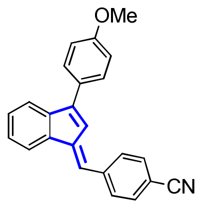
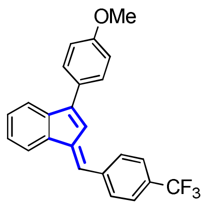
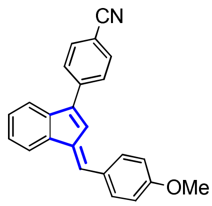
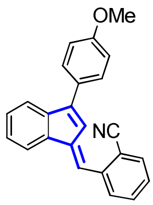
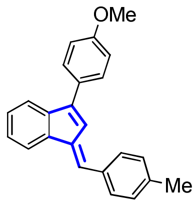
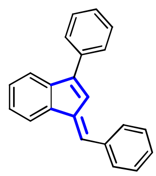
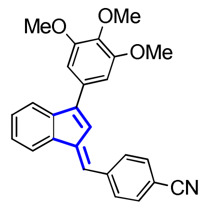
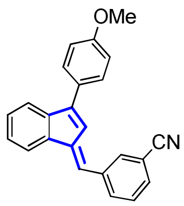
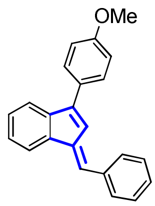
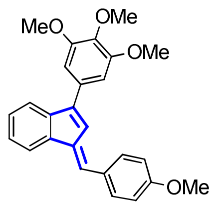
6-*endo-dig* / 5-*exo-dig* Cyclization products [a]

Entry	Product yield[b]		Entry	Product yield[b]	
1	 **2a**: 89%	 **3a**: 7%	6	 **2f**: 92%	 **3f**: -
2	 **2b**: 87%	 **3b**: 10%	7	 **2g**: 90%	 **3g**: -
3	 **2c**: 73%	 **3c**: 7%	8	 **2h**: 96%	 **3h**: -
4	 **2d**: 70%	 **3d**: 10%	9	 **2i**: 98%	 **3i**: -
5	 **2e**: 90%	 **3e**: -	10	 **2j**: 73%	 **3j**: 9%

[a] Reaction conditions are: Enyne 1 (0.6 mmol), $(PPh_3)AuNTf_2$ (5 mol%), THF (1 ml) at 70 °C for 3 h under argon.
[b] Isolated yields.

Table 3. . Intramolecular hydroarylation of aromatic enynes **1** under Pd-catalysis



5-*exo-dig* Cyclization products [a]							
Entry	Product yield[b]	Entry	Product yield[b]	Entry	Product yield[b]	Entry	Product yield[b]
1	 **3a**: 77%	4	 **3d**: 79%	7	 **3g**: 81%		
2	 **3b**: 60%	5	 **3e**: 80%	8	 **3h**: 84%	10	 **3j**: 76%
3	 **3c**: 57%	6	 **3f**: 88%	9	 **3i**: 72%		

[a] Reactions conditions: Enyne **1** (0.6 mmol), PdI_2 (10 mol%), Dppp (20 mol%), Cs_2CO_3 (1 eq), 1,4-Dioxane (2 ml) at 150 °C for 15 h in a sealed tube.
[b] Isolated yields.

cyclization product **3a** in a good 77% yield (entry 14). Finally, screening of phosphine-ligands (entries 14-19) demonstrates the supremacy of bidentate ligand dppp (entry 14) in comparison to ferrocene (entries 16-18) or biaryl-type ligand (entry 19). Also, we found that the use of Gevorgyan conditions with enyne **1** were not nor stero- nor regio-selective (entry 17), as a mixture of compounds **2a** and **3a** was obtained and the benzofulvene compound was obtained as a mixture of *E* and *Z* isomers (70/30 *E*/*Z*). It should be noted that our new palladium-catalyzed cycloisomerization conditions of **1a** (entry 14) is stereoselective, giving exclusively the (*E*)-isomer **3a**, as was determined by RMN 2D (NOESY experiments).

Once the influence of the nature of the catalyst as well as the reaction conditions on the regioselectivity of the cycloisomerization of **1a** were defined, we used the above optimized conditions (entries 5 and 14) on different substitution patterns on the aromatic enynes **1** (Tables 2 and 3).

Au catalysis (Table 2): The examples compiled in Table 2 show the generality of this cycloisomerization reaction catalyzed by PPh_3AuNTf_2 complex. Various substituted naphthalene derivatives **2** were formed with isolated yields up to 98% (compounds **2a-j**). The reaction worked selectively towards the 6-*endo-dig* cyclization pattern regardless to the electronic effects of the substituents on the aromatic nucleus of the alkene moiety.

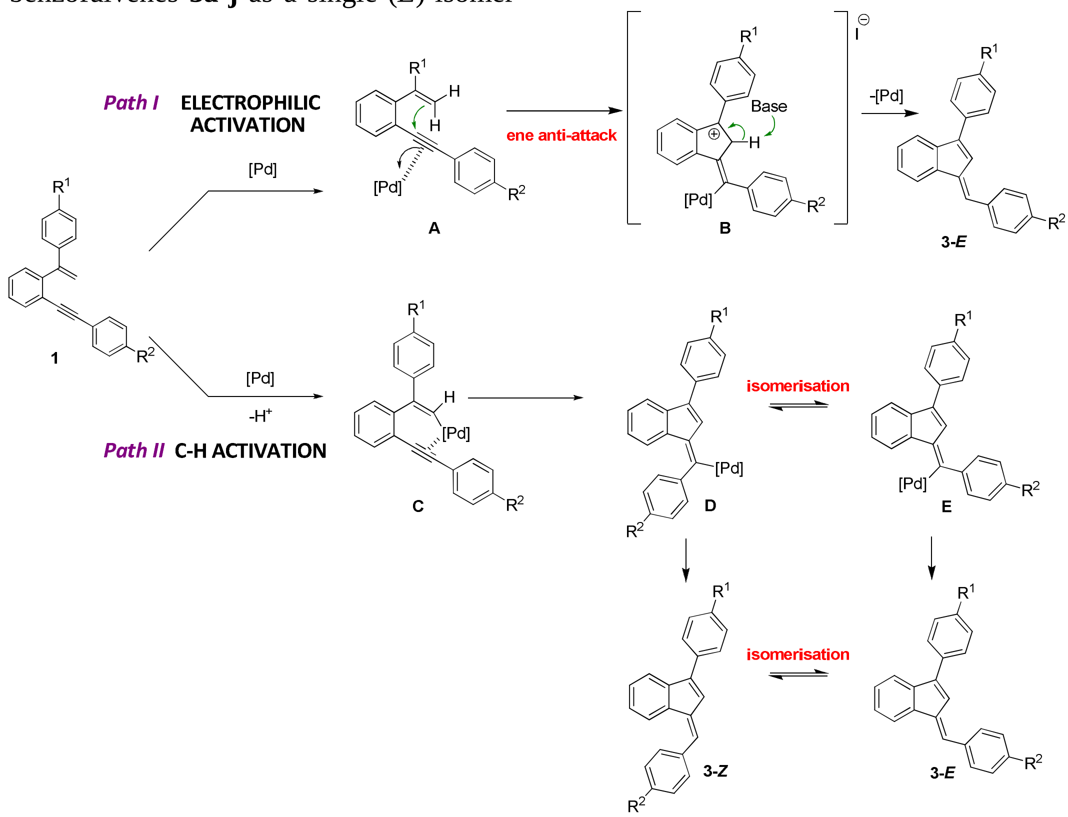
Aromatic substituents on the alkyne moiety had somewhat more effect on the cycloisomerization reaction selectivity. In fact, the presence of electron-rich or electron-neutral aromatic groups on the alkyne provided exclusively the corresponding 6-*endo-dig* ring closure products **2e-i**. However, the presence of electron-poor aromatic groups slightly diminished the yields of the 6-*endo-dig* ring closure compounds **2a-d**, and **2j** in favor of the corresponding 5-*exo-dig* products **3a-d**, and **3j**, but with yields never exceeding 10%. These results clearly demonstrated that electronic effects on the alkyne moiety, play a crucial role in the regioselectivity outcome.[16] The substituent's position was studied as well, and very good yields were also obtained with aromatic enyne substrates having various groups, such as OMe, Me, CF_3, CN in *meta*-, *ortho*- and *para*-positions.

Pd catalysis (Table 3): With the optimized conditions in hand (Table 1, entry 14), we next explored the generality of this transformation. In contrast to PPh_3AuNTf_2 complex, the PdI_2/dppp catalytic system triggered the exclusive 5-*endo-dig* cyclization leading to the benzofulvene derivatives **3a-j** in good to excellent yields, regardless the electronic nature of the aromatic substituent on the alkene and the alkyne moieties! (Table 3).[17] Importantly, the cyclization of all aromatic enynes **1a-j** proceeded in a *trans*-stereoselective manner producing benzofulvenes **3a-j** as a single (*E*)-isomer.[18] Various groups, such as CN, F, CF_3 and OMe, were perfectly tolerated under the optimized conditions. Finally, the substituent's position had little effect on the reaction outcome; the *para* position facilitated the reaction course giving **3a** in 77%, while the yields were slightly lower with substrates possessing a CN group at the *ortho* and *meta*-position, leading to **3b** and **3c** in yields of 60% and 57%, respectively.

In the presence of an alkyl group at the terminal position of the alkyne or the internal position of the alkene, no cyclization was observed.[19]

Mechanistic investigations for exclusive 5-*exo-dig* cyclization of aromatic enynes under palladium catalysis.

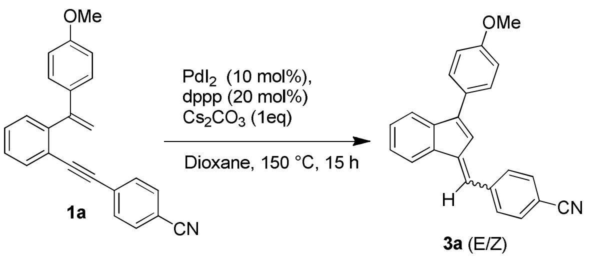
If cycloisomerization of enyne derivatives based on Au-catalysis have grown into a major field of experimental as well as theoretical research,[20] mechanistic investigations for palladium catalyzed 5-*exo-dig* cyclization of enynes were not extensively studied. At this stage of the study, we are not able to confirm if the Pd catalyzed cycloisomerization of enynes **1** evolves either by π or by C-H activation.



Scheme 1. Proposed mechanism for the 5-*exo-dig* cyclization of aroamtic enynes under palladium catalysis.

In contrast to the previous work of Gevorgyan[7b] on the cyclization of *o*-alkynyl biphenyls, which proceeds with a *cis*-selectivity, our study on the cyclization of aromatic enynes **1** showed that the reaction formally occurred with a *trans*-selectivity. On the basis of the stereochemistry of compounds **3** formed (Table 2) and the literature reports,[8, 16a] it seems that the formation of **3** may be rationalized *via* an electrophilic cyclization of aromatic enynes **1** (Scheme 1, path I). In this pathway, the palladium catalyst acts as a Lewis acid. It initiates the reaction by coordination to the triple bond (complex **A**); the resulting activated alkyne could undergo nucleophilic attack by alkene moiety to form alkenylpalladium species **B**, which would produce the final product and regenerate the catalyst.

In order to better understand this transformation, we performed a kinetic study in order to examine whether the (*E*)-isomer is the only product formed during the reaction. To this end, the cyclization of **1a** was conducted under optimized conditions and the reaction progress was followed depending on the reaction time. As illustrated in Scheme 2, at the beginning of this transformation (90 min), in addition to the expected benzofulvene *E*-**3a**, a significant amount (20%) of its isomer *Z*-**3a** was formed, and then disappeared at the end of the reaction (15 h).



Entry	Time (min)	*E*-**3a**/*Z*-**3a**
1	90	80/20
2	180	85/15
3	240	90/10
4	540	95/5
5	900	100/0

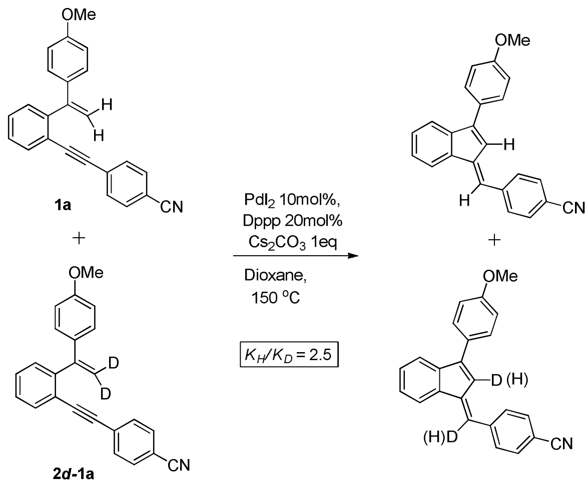
Scheme 2. *E*/*Z* distribution of **3a** during the cyclization reaction.

This result suggests that *Z*-**3a** is unstable under the optimized conditions and isomerizes to the thermodynamically more stable isomer *E*-**3a.**[21] The existence of both isomers *E*/*Z* of compound **3a** at the early stage of the reaction strongly suggests that the pathway II (Scheme 1) might be considered more likely involving the following steps: (*i*) activation of C–H bond to form σ-alkenylpalladium intermediate **C**, (*ii*) migratory insertion to the triple bond would form species **D**, and (*iii*) protiodepalladation of **D** gives *Z*-benzofulvene **3** which then isomerizes into its *E*-isomer. One can note isomerisation may also occur between alkenylpalladium species **D** and **E** as illustrated in Scheme 1.

In view to support this suggested mechanism, kinetic isotope effect studies were performed (Scheme 3). Intermolecular competition between aromatic enyne **1a**, together with its deuterated analogue **2*d*-1a** under our standard conditions revealed a substantial intermolecular kinetic isotope effect (k_H/k_D = 2.5). These data are in a range of the isotope effects observed for the reactions proceeding *via* the Pd-catalyzed aromatic C–H activation.

In order to support this C–H activation path, we then realized a computational study.

Computational studies. The mechanism of the cyclization reaction of enyne **1h**, catalyzed by palladium, was studied computationally at the DFT level. We first estimated cyclization barrier following both electrophilic activation (path I) and C-H activation (path II) pathways envisioned in Scheme 1.[22] Various coordination spheres around Pd have been studied ([Pd] = PdI_2PMe_3, $PdI(PMe_3)_2^+$,

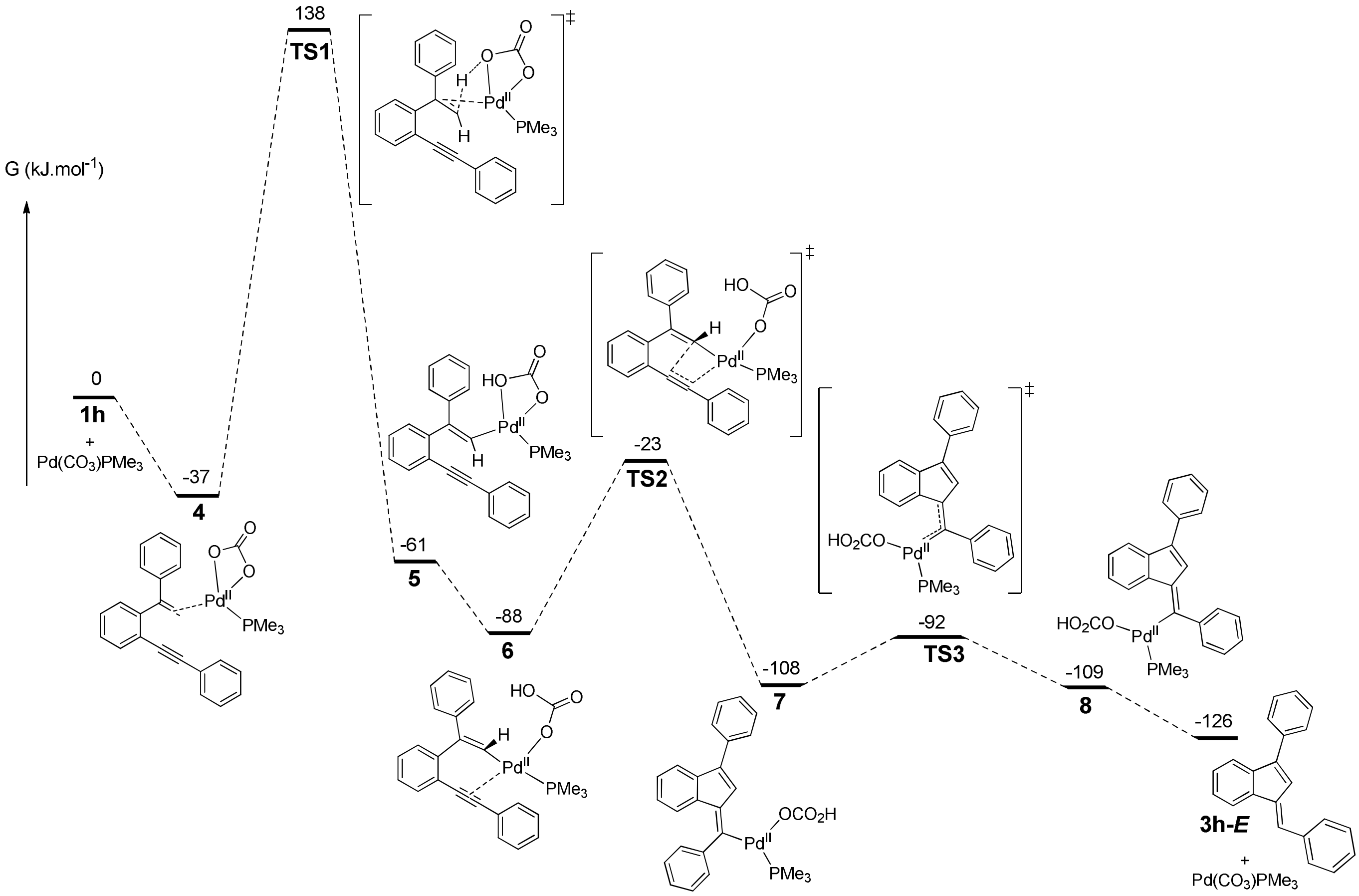


Scheme 3. ^{1}H/^{2}H intermolecular kinetic isotope effect experiments.

$Pd(CO_3)(PMe_3)_2$ and $Pd(CO_3)PMe_3$) to explore a large set of catalytic species. Among them, $Pd(CO_3)PMe_3$ gives the lowest cyclization transition state for the electrophilic activation pathway. An even lower energy transition state is obtained for the 5-*exo-dig* cyclization following the C-H activation pathway with the same Pd-complex. With this catalytic system, the whole reaction mechanism for the C-H activation pathway has been investigated to confirm its reliability (Scheme 4). Our calculations indicate that the activation of C-H bond to form intermediate **6** (**C** in Scheme 1) could be decomposed in three steps: *i*) first coordination of the catalyst to the double bond (**4**); *ii*) intramolecular-deprotonation of the CH_2 terminal group by the carbonate ligand, via transition state **TS1**, which produces intermediate **5**; *iii*) formation of the palladium π complex **6**. Next, the 5-*exo-dig* cyclization step leads easily to intermediate **7** (**D** in Scheme 1), which can isomerize to **8** via transition-state **TS3**. Finally, intramolecular protiodepalladation of **8** leads to *E*-benzofulvene **3h**. This DFT study shows that the limiting step clearly is **TS1** (CH-activation), this is in complete agreement with the experimental results.

Conclusion

In conclusion, we report a general approach for converting aromatic enynes into phenylnaphthalenes **2** or benzofulvenes **3** depending on the nature of the catalytic system used. In fact, we were able to control the regioselectivity of aromatic enynes cycloisomerization process. $Ph_3PAuNTf_2$ was the best catalyst to promote, via an electrophilic activation, mainly 6-*endo-dig* cyclization leading to a variety of phenylnaphthalene derivatives. Moreover, a fine tuning of other Lewis acids, ligands and reaction conditions led us to discover that PdI_2/dppp as a catalytic system guided an exclusive 5-*exo-dig* cyclization pattern and a subsequent formation of (*E*)-benzofulvenes. These results were obtained regardless to the electronic nature of substituents on alkene and alkyne moieties. KIE and DFT studies led us to propose a C - H activation mechanism for this palladium catalyzed transformation.



Scheme 4. Gibbs free energies for the Pd-catalyzed cyclization of aromatic enyne **1h**.

Experimental Section

General procedure for the Gold(I)-catalyzed cyclization. To a solution of the corresponding enyne (1 equiv) in 3 ml of anhydrous THF under argon was added 0.05 equiv of PPh_3AuNTf_2. The reaction mixture was stirred at reflux until total conversion (3 hours). Then, the solvent was evaporated under reduced pressure to give the crude product which was purified by flash chromatography on silica gel.

4-(4-(4-methoxyphenyl)naphthalen-2-yl)benzonitrile (2a). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 90/10) to give 90 mg of **2a** (0.27 mmol; yield 89%); colorless oil; M= 335.4 g.mol-1; R_f = 0.72 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 2224, 1602, 1514, 1498, 1462, 1288, 1244, 1177, 1110, 1033; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.05 (d, J = 1.5 Hz, 1H), 7.96 (t, J = 6.8 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.4 Hz, 2H), 7.64 (d, J = 1.9 Hz, 1H), 7.60 – 7.41 (m, 4H), 7.07 (d, J = 8.7 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.3 (C), 145.4 (C), 141.2 (C), 135.9 (C), 134.1 (C), 132.7 (2CH), 132.6 (C), 131.7 (C), 131.1 (2CH), 128.9 (CH), 128.0 (2CH), 126.9 (CH), 126.7 (CH), 126.1 (C), 125.9 (CH), 125.8 (CH), 119.0 (C), 114.0 (2CH), 111.0 (C), 55.5 (OCH_3); HRMS (ESI) $(M + Na)^+$ *m/z* calculated for $C_{24}H_{17}NNaO$ 358.1202 found 358.1188.

2-(4-(4-methoxyphenyl)naphthalen-2-yl)benzonitrile (2b). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 90/10) to give 90 mg of **2b** (0.26 mmol; yield 87%); yellow oil; M= 335.4 $g.mol^{-1}$; R_f = 0.61 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 2224, 1609, 1514, 1288, 1245, 1179, 1108, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.06 – 7.96 (m, 3H), 7.81 (dd, J = 7.7, 0.8 Hz, 1H), 7.67 (d, J = 3.8 Hz, 3H), 7.63 (d, J = 1.8 Hz, 1H), 7.60 – 7.42 (m, 4H), 7.07 (d, J = 8.7 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.3 (C), 145.5 (C), 140.7 (C), 135.1 (C), 133.9 (CH), 133.9 (C), 132.9 (CH), 132.7 (C), 131.7 (C), 131.3 (2CH), 130.4 (CH), 129.0 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.9 (CH), 126.6 (CH), 126.1 (CH), 118.9 (C), 114.0 (2CH), 111.7 (C), 55.5 (OCH_3); HRMS (ESI) $(M + Na)^+$ *m/z* calculated for $C_{24}H_{17}NNaO$ 358.1202 found 358.1191.

3-(4-(4-methoxyphenyl)naphthalen-2-yl)benzonitrile (2c). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 90/10) to give 70 mg of **2c** (0.22 mmol; yield 73%); yellow oil; M= 335.4 g.mol^{-1}; R_f = 0.72 (Cyclohexane/ EtOAc 70/30); IR (film, cm^{-1}): 3372, 2228, 2037, 1609, 1575, 1515, 1464, 1401, 1288, 1245, 1178, 1034, 908; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.06 – 8.00 (m, 2H), 7.96 (m, 3H), 7.70 – 7.52 (m, 4H), 7.51 – 7.40 (m, 3H), 7.07 (d, *J* = 8.7 Hz, 2H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.3 (C), 142.3 (C), 141.2 (C), 135.6 (C), 134.2 (C), 132.6 (C), 131.7 (CH), 131.6 (C), 131.2 (2CH), 131.0 (CH), 130.8 (CH), 129.7 (CH), 128.8 (CH), 126.8 (CH), 126.7 (CH), 126.1 (CH), 125.9 (CH), 125.5 (CH), 118.9 (C), 114.0 (2CH), 113.1 (C), 55.5 (OCH_3); HRMS (ESI) $(M + Na)^+$ *m/z* calculated for $C_{24}H_{17}NNaO$ 358.1202 found 358.1194.

1-(4-methoxyphenyl)-3-(4-(trifluoromethyl)-phenyl)-naphthalene (2d). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 95/5) to give 70 mg of **2d** (0.18 mmol; yield 70%); yellow oil; M= 378.4 g.mol^{-1}; R_f = 0.65 (Cyclohexane/EtOAc 80/20); IR (film, cm^{-1}): 3493, 3454, 3433, 3416, 3316, 3267, 3172, 2331, 2278, 2171, 2130, 2060, 2043, 2021, 1938, 1612, 1514, 1324, 1288, 1246, 1165, 1126, 1109, 1071, 1034; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.06 (d, *J* = 1.2 Hz, 1H), 7.96 (t, *J* = 8.1 Hz, 2H), 7.86 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H), 7.67 (d, *J* = 1.8 Hz, 1H), 7.58 – 7.41 (m, 4H), 7.07 (d, *J* = 8.6 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 159.3 (C), 144.7 (C), 141.1 (C), 136.7 (C), 134.2 (C), 132.9 (C), 131.6 (C), 131.2 (2CH), 129.6 (C, $^2J_{C\text{-}F}$ = 32.5 Hz), 128.8 (CH), 127.8 (2CH), 126.7 (CH), 126.6 (CH), 126.3 (CH), 126.2 (CH), 125.9 (2CH, $^3J_{C\text{-}F}$ = 3.6 Hz), 125.8 (CH), 124.5 (C, $^1J_{C\text{-}F}$ = 271.9 Hz), 114.0 (2CH), 55.6 (OCH_3); ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm) -60.4, -60.5, -60.6; HRMS (ESI) $(M + H)^+$ *m/z* calculated for $C_{24}H_{18}F_3O$ 379.1310 found 379.1308.

1-(4-methoxyphenyl)-3-*p*-tolylnaphthalene (2e). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 90/10) to give 90 mg of **2e** (0.28 mmol; yield 90%); oil; M= 324.42 g.mol^{-1}; R_f = 0.86 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 1609, 1513, 1287, 1243, 1178, 1034; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.05 (d, *J* = 1.4 Hz, 1H), 7.96 (dd, *J* = 8.0, 4.3 Hz, 2H), 7.71 (d, *J* = 1.9 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.57 – 7.39 (m, 4H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.7 Hz, 2H), 3.92 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.1 (C), 140.5 (C), 138.0 (C), 138.0 (C), 137.1 (C), 134.4 (C), 133.1 (C), 131.2 (2CH), 131.0 (C), 129.6 (2CH), 128.6 (CH), 127.3 (2CH), 126.6 (CH), 126.1 (CH), 126.0 (CH), 125.9 (CH), 124.8 (CH), 113.8 (2CH), 55.2 (OCH_3), 21.1 (CH_3); HRMS (ESI) $(M + H)^+$ *m/z* calculated for $C_{24}H_{21}O$ 325.1592 found 325.1590.

1-(4-methoxyphenyl)-3-phenylnaphthalene (2f). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 90/10) to give 92 mg of **2f** (0.30 mmol ; yield 92%); oil; M= 310.4 g.mol^{-1}; R_f = 0.72 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 1513, 1244, 1179, 1032; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.07 (d, *J* = 1.5 Hz, 1H), 8.01 – 7.94 (m, 2H), 7.79 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.73 (d, *J* = 1.9 Hz, 1H), 7.58 – 7.37 (m, 7H), 7.08 (d, *J* = 8.8 Hz, 2H), 3.93 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.2 (C), 141.1 (C), 140.6 (C), 138.2 (C), 134.4 (C), 133.2 (C), 131.3 (2CH), 129.0 (2CH), 128.7 (CH), 127.5 (2CH), 126.8 (CH), 126.3 (CH), 126.1 (CH), 126.1 (CH), 125.2 (CH), 113.9 (2CH), 55.4 (OCH_3); HRMS (ESI) $(M + H)^+$ *m/z* calculated for $C_{23}H_{19}O$ 311.1436 found 311.1435.

4-(3-(4-methoxyphenyl)naphthalen-1-yl)benzonitrile (2g). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 90/10) to give 90 mg of **2g** (0.27 mmol; yield 90%); oil; M= 335.40 g.mol^{-1}; R_f = 0.82 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 2225, 1607, 1513, 1286, 1244,, 1179, 1031; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.07 (s, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.78 (t, *J* = 7.1 Hz, 3H), 7.70 (s, 1H), 7.68 – 7.60 (m, 4H), 7.55 (t, *J* = 7.0 Hz, 1H), 7.46 (dd, *J* = 11.1, 4.1 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.6 (C), 145.7 (C), 138.8 (C), 137.7 (C), 134.3 (C), 132.9 (C), 132.2 (2CH), 130.9 (2CH), 129.9 (C), 128.8 (CH), 128.5 (2CH), 126.6 (CH), 126.6 (CH), 126.5 (CH), 125.7 (CH), 125.1 (CH), 119.0 (C), 114.5 (2CH), 111.3 (C), 55.5 (OCH_3); HRMS (ESI) $(M + H)^+$ *m/z* calculated for $C_{24}H_{18}NO$ 336.1388 found 336.1386.

3-(4-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl)-naphthalene (2i). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 90/10) to give 100 mg of **2i** (0.24 mmol; yield 98%); yellow oil; M= 400.47 g.mol^{-1}; R_f = 0.55 (Cyclohexane/EtOAc 70/30); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.02 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 2H), 7.71 (dd, *J* = 5.5, 2.9 Hz, 3H), 7.48 (m, 2H), 7.04 (d, *J* = 8.6 Hz, 2H), 6.77 (s, 2H), 3.98 (s, 3H), 3.90 (s, 6H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.3 (C), 153.0 (2C), 140.7 (C), 137.5 (C), 137.3 (C), 136.4 (C), 134.2 (C), 133.1 (C), 130.5 (C), 128.5 (CH), 128.4 (2CH), 126.2 (2CH), 125.9 (CH), 125.8 (CH), 124.6 (CH), 114.3 (2CH), 107.2 (2CH), 60.9 (OCH_3), 56.11 ($2OCH_3$), 55.2 (OCH_3); HRMS (ESI) $(M + H)^+$ *m/z* calculated for $C_{26}H_{25}O_4$ 401.1753 found 401.1751.

4-(4-(3,4,5-trimethoxyphenyl)naphthalen-2-yl)benzonitrile (2j). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 90/10) to give 70 mg of **2j** (0.18 mmol; yield 73%); yellow oil; M= 395.45 g.mol^{-1}; R_f = 0.58 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 3462, 3411, 3356, 3301, 3208, 3127, 2861, 2485, 2362, 2306, 2195, 2102, 2034, 1962, 1604, 1508, 1399, 1336, 1181, 1127, 1007; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 8.08 (d, *J* = 1.5 Hz, 1H), 8.02 – 7.94 (m, 2H), 7.87 (d, *J* = 8.6 Hz, 2H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 1.9 Hz, 1H), 7.54 (m, 2H), 6.74 (s, 2H), 3.96 (s, 3H), 3.89 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 153.3 (2C), 145.4 (C), 141.6 (C), 137.7 (C), 135.9 (C), 135.9 (C), 134.1 (C), 132.7 (2CH), 131.6 (C), 128.9 (CH), 128.1 (2CH), 127.1 (CH), 126.8 (CH), 126.2 (CH), 126.1 (CH), 125.7 (CH), 119.0 (C), 111.1 (C), 107.3 (2CH), 61.1 (OCH_3), 56.3 ($2OCH_3$); HRMS (ESI) $(M + H)^+$ *m/z* calculated for $C_{26}H_{22}NO_3$ 396.1600 found 396.1598.

General procedure for the Pd(II)-catalyzed cyclization. In a sealed tube and under argon inlet, the enyne (1 equiv), PdI_2 (0.1 equiv), Dppp (0.2 equiv) and Cs_2CO_3 (1 equiv) were mixed in 2 ml of dioxane. The reaction vessel was then capped with a pressure screw cap and the reaction mixture was stirred at 150 °C for 15 hours. The crude reaction mixture was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through celite. Then, the solvent was evaporated under reduced pressure to give the crude product which was purified by flash chromatography on silica gel.

(*E*)-4-((3-(4-methoxyphenyl)-1H-inden-1-ylidene)-methyl)benzonitrile (3a). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 95/5) to give 80 mg of **3a** (0.23 mmol; yield 77%); yellow oil; M= 335.40 g.mol-1; R_f = 0.74 (Cyclohexane/ EtOAc 70/30); IR (film, cm^{-1}): 3468, 3453, 3434, 3407, 3391, 3377, 3338, 3275, 3229, 3111, 3063, 3047, 2999, 2947, 2930, 2542, 2271, 2189, 2172, 2132, 2091, 2052, 2030, 2010, 1984, 1928, 1605, 1501, 1342, 1287, 1251, 1178, 1032; ^{1}H NMR (300 MHz, CDCl3) δ (ppm) 7.78 – 7.68 (m, 5H), 7.65 (d, J = 8.8 Hz, 2H), 7.61 – 7.54 (m, 1H), 7.38 (s, 1H), 7.36 – 7.28 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 6.93 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.2 (C), 149.3 (C), 142.2 (C), 142.0 (C), 141.2 (C), 138.7 (C), 132.5 (2CH), 130.6 (2CH), 129.0 (2CH), 128.3 (CH), 127.8 (C), 126.1 (CH), 124.5 (CH), 121.1 (CH), 120.9 (CH), 119.8 (CH), 119.0 (C), 114.4 (2CH), 111.3 (C), 55.5 (OCH_3); HRMS (ESI) $(M + Na)^+$ *m/z* calculated for $C_{24}H_{17}NNaO$ 358.1202 found 358.1182.

(*E*)-2-((3-(4-methoxyphenyl)-1*H*-inden-1-ylidene)-methyl)benzonitrile (3b). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 95/5) to give 60 mg of **3b** (0.17 mmol; yield 60%); yellow oil; M= 335.40 g.mol^{-1}; R_f = 0.61 (Cyclohexane/ EtOAc 70/30); IR (film, cm^{-1}): 3440

3416, 3400, 3378, 3352, 3296, 3268, 3241, 3217, 3142, 3121, 3036, 2990, 2946, 2702, 2361, 2234, 2184, 2157, 2121, 2061, 2034, 2019, 1988, 1964, 1253; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.83 (dd, *J* = 9.7, 5.0 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.61 (m, 5H), 7.46 – 7.29 (m, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.87 (s, 1H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.2 (C), 149.4 (C), 143.0 (C), 141.3 (C), 140.6 (C), 138.5 (C), 133.3 (CH), 132.76 (CH), 131.00 (CH), 129.02 (2CH), 128.37 (CH), 128.10 (CH), 127.82 (C), 126.2 (CH), 121.9 (CH), 121.1 (CH), 120.8 (CH), 120.2 (CH), 117.9 (C), 114.3 (2CH), 113.0 (C), 55.5 (OCH_3); HRMS (ESI) (M + Na)$^+$ *m/z* calculated for $C_{24}H_{17}NNaO$ 358.1202 found 358.1189.

(*E*)-3-((3-(4-methoxyphenyl)-1*H*-inden-1-ylidene)-methyl)benzonitrile (3c). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 95/5) to give 70 mg of **3c** (0.21 mmol; yield 57%); yellow oil; M= 335.40 g.mol^{-1}; R_f = 0.69 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 3484, 3462, 3440, 3336, 3254, 3225, 2956, 2278, 2208, 1607, 1593, 1513, 1441, 1342, 1287, 1249, 1178, 1107, 1033; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.89 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.77 – 7.71 (m, 1H), 7.66 (d, *J* = 8.8 Hz, 2H), 7.59 (m, 2H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.39 – 7.27 (m, 3H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.92 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.2 (C), 149.0 (C), 141.5 (C), 141.2 (C), 138.7 (C), 138.6 (C), 134.2 (CH), 133.3 (CH), 131.2 (CH), 129.6 (CH), 129.1 (2CH), 128.2 (CH), 127.8 (C), 126.0 (CH), 124.0 (CH), 120.9 (CH), 120.8 (CH), 119.7 (CH), 118.6 (C), 114.3 (2CH), 113.2 (C), 55.5 (OCH_3); HRMS (ESI) (M + Na)$^+$ *m/z* calculated for $C_{24}H_{17}NNaO$ 358.1202 requires 358.1198.

(*E*)-3-(4-methoxyphenyl)-1-(4-(trifluoromethyl)-benzylidene)-1*H*-indene (3d). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 95/5) to give 79 mg of **3d** (0.21 mmol; yield 79%); yellow oil; M= 378.39 g.mol^{-1}; R_f = 0.77 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 3456, 3198, 2971, 2153, 1606, 1502, 1462, 1419, 1321, 1249, 1177, 1162, 1124, 1108, 1066, 1033, 1015, 931; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.80 – 7.56 (m, 8H), 7.45 (s, 1H), 7.38 – 7.29 (m, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.98 (s, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.1 (C), 148.6 (C), 141.4 (C), 141.3 (C), 140.9 (C), 138.8 (C), 130.3 (2CH), 130.0 (C), 124.3 (C, $^1J_{C-F}$ = 271.7 Hz), 129.6 (C), 129.0 (2CH), 128.0 (CH), 125.9 (CH), 125.7 (2CH, $^3J_{C-F}$ = 3.8 Hz), 125.3 (CH), 121.4 (CH), 120.7 (CH), 119.7 (CH), 114.3 (2CH), 55.5 (OCH_3); ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm) -60.4, -60.5, -60.6; HRMS (ESI) (M + Na)$^+$ *m/z* calculated for $C_{24}H_{17}F_3NaO$ 401.1129 found 401.1135.

(*E*)-3-(4-methoxyphenyl)-1-(4-mehylbenzylidene)-1*H*-indene (3e). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 90/10) to give 80 mg of **3e** (0.25 mmol; yield 80%); yellow oil; M= 324.42 g.mol^{-1}; R_f = 0.85 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 3401, 3302, 3279, 3252, 3232, 2839, 2556, 2386, 2324, 2303, 2285, 2154, 2109, 2076, 2036, 2015, 2580, 1547, 1503, 1458, 1412, 1342, 1300, 1236, 1182, 1127, 1074, 1007; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.79 – 7.71 (m, 1H), 7.64 (d, *J* = 8.7 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 3H), 7.45 (s, 1H), 7.31- 7.19 (m, 4H),7.08 (s, 1H), 6.99 (d, *J* = 8.7 Hz, 2H), 3.85 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.9 (C), 146.8 (C), 140.9 (C), 139.3 (C), 138.6 (C), 138.6 (C), 134.5 (C), 130.4 (2CH), 129.6 (2CH), 129.0 (2CH), 128.6 (C), 127.8 (CH), 127.3 (CH), 125.5 (CH), 122.3 (CH), 120.4 (CH), 119.3 (CH), 114.3 (2CH), 55.5 (OCH_3), 21.5 (CH_3); HRMS (ESI) (M + H)$^+$ *m/z* calculated for $C_{24}H_{21}O$ 325.1587 found 325.1577.

(*E*)-1-benzildene-3-(4-méthoxyphenyl)-1*H*-indene (3f). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 95/5) to give 90 mg of **3f** (0.27 mmol; yield 88%); yellow oil; M= 310.39 g.mol^{-1}; R_f = 0.72 (Cyclohexane/ EtOAc 80/20); IR (film, cm^{-1}): 2999, 2838, 2218, 1648, 1605, 1582, 1530, 1502, 1456, 1416, 1374, 1338, 1315, 1251, 1226, 1205, 1177, 1158, 1129, 1051, 1034, 951; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.79 (dd, *J* = 5.7, 2.9 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 4H), 7.64 – 7.57 (m, 1H), 7.47 (dd, *J* = 14.6, 7.4 Hz, 3H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 3.3 Hz, 2H), 7.11 (s, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 159.9 (C), 147.3 (C), 141.1 (C), 139.4 (C), 139.2 (C), 137.4 (C), 130.4 (2CH), 129.0 (2CH), 128.9 (2CH), 128.4 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 125.6 (CH), 122.2 (CH), 120.5 (CH), 119.5 (CH), 114.3 (2CH), 55.5 (OCH_3); HRMS (ESI) (M + H)$^+$ *m/z* calculated for $C_{23}H_{19}O$ 311.1430 found 311.1428.

(*E*)-4-(1-(4-methoxybenzilidene)-1*H*-inden-3-yl)benzonitrile (3g). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 95/5) to give 80 mg of **3g** (0.24 mmol; yield 81%); yellow oil; M= 335.40 g.mol^{-1}; R_f = 0.80 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 3457, 3426, 3206, 2226, 2167, 2053, 2034, 1597, 1511, 1462, 1446, 1343, 1304, 1256, 1174, 1031, 910; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.83 – 7.69 (m, *J* = 8.3 Hz, 5H), 7.63 (d, *J* = 8.6 Hz, 2H), 7.56 (s, 1H), 7.53 (d, *J* = 3.1 Hz, 1H), 7.32 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.23 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.5 (C), 144.7 (C), 140.7 (C), 139.5 (C), 139.0 (C), 136.9 (C), 132.6 (2CH), 132.1 (2CH), 130.3 (CH), 129.6 (C), 128.3 (2CH), 127.3 (CH), 125.9 (CH), 125.1 (CH), 120.0 (CH), 119.5 (CH), 119.1 (C), 114.6 (2CH), 111.3 (C), 55.5 (OCH_3); HRMS (ESI) (M + Na)$^+$ *m/z* calculated for $C_{24}H_{17}NNaO$ 358.1202 found 358.1196.

(*E*)-1-(4-methoxybenzylidene)-3-(3,4,5-trimethoxyphenyl)1*H*-indene (3i). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 95/5) to give 100 mg of **3i** (0.25 mmol; yield 72%); yellow oil; M= 400.47 g.mol^{-1}; R_f = 0.53 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 2934, 2836, 2221, 1602, 1573, 1510, 1498, 1463, 1448, 1414, 1351, 1304, 1255, 1235, 1175, 1126, 1060, 1032, 1007; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.81 – 7.76 (m, 1H), 7.65 (d, *J* = 8.8 Hz, 2H), 7.62 – 7.57 (m, 1H), 7.49 (s, 1H), 7.32 (dd, *J* = 6.1, 2.4 Hz, 2H), 7.13 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.91 (s, 2H), 3.94 (s, 6H), 3.93 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 160.2 (C), 153.6 (2C), 146.9 (C), 140.5 (C), 139.2 (C), 138.3 (C), 137.3 (C), 131.9 (2CH), 131.7 (C), 129.9 (C), 128.4 (CH), 127.1 (CH), 125.5 (CH), 122.8 (CH), 120.3 (CH), 119.3 (CH), 114.5 (2CH), 105.1 (2CH), 61.1 (OCH_3), 56.4 ($2OCH_3$), 55.5 (OCH_3); HRMS (ESI) (M + H)$^+$ *m/z* calculated for $C_{26}H_{25}O_4$ 401.1747 found 401.1728.

(*E*)-4-((3-(3,4,5-trimethoxyphenyl)-1*H*-inden-1-ylidene)methyl)benzo- nitrile (3j). The crude residue was purified by flash chromatography on silica gel (Cyclohexane/EtOAc 95/5) to give 80 mg of **3j** (0.23 mmol; yield 76%); yellow oil; M= 395.45 g.mol^{-1}; R_f = 0.58 (Cyclohexane/EtOAc 70/30); IR (film, cm^{-1}): 3470, 3411, 3395, 3373, 3356, 3329, 3281, 3262, 3120, 3076, 3058, 2877, 2604, 2566, 2408, 2299, 2271, 2160, 2121, 2032, 2015, 1995, 1974, 1953, 1938, 1601, 1576, 1500, 1448, 1415, 1351, 1238, 1126, 1007, 909; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 7.79 – 7.74 (m, 1H), 7.72 (s, 4H), 7.58 (dd, *J* = 6.1, 2.1 Hz, 1H), 7.44 (d, *J* = 0.6 Hz, 1H), 7.39 – 7.31 (m, 2H), 6.94 (d, *J* = 0.6 Hz, 1H), 6.88 (s, 2H), 3.93 (s, 6H), 3.92 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 153.7 (2C), 149.8 (C), 141.9 (C), 141.8 (C), 141.1 (C), 138.9 (C), 138.6 (C), 132.6 (2CH), 130.9 (C), 130.6 (2CH), 128.4 (CH), 126.3 (CH), 125.4 (CH), 121.8 (CH), 120.8 (CH), 119.9 (CH), 118.9 (C), 111.5 (C), 105.1 (2CH), 61.1 (OCH_3), 56.5 ($2OCH_3$); HRMS (ESI) (M + Na)$^+$ *m/z* calculated for $C_{26}H_{21}NNaO_3$ 418.1414 found 418.1394.

Computational methods. Calculations have been carried out with the Gaussian09 package of programs.[23] Full geometry optimizations of all compounds were carrried out with the use of the B3LYP.[24] density functional level of theory with the following basis set noted BS1. A 6-31G(d) basis set was employed for the first- (H), second- (C, O), and third-row (P) elements. The standard LANL2DZ small-core relativistic effective-core potential with a valence shell of double-ζ quality was used on palladium and iodine.[25] To get accurate energies and Gibbs free energies, the SCF convergence criterion has been systematically tightened to 10^{-8} a.u., and the force minimizations were carried out until the rms force becomes smaller than (at least) 1 x 10^{-5} a.u. Each stationary point has been characterized with frequency analysis and shows the correct number of negative eigenvalues (0 for a local minimum and one for a transition state). Intrinsic reaction coordinate (IRC) calculations have been performed to ascertain the identity of the transition structure under consideration. The validity of this level of calculation has been demonstrated in previous studies on Pd(II) complexes.[26] Zero-point vibrational energy corrections and thermal corrections to Gibbs free energy were evaluated at the B3LYP/BS1 level at 423.15K according to experimental conditions. Energies were evaluated with the M06 method,[27] 6-311++G(2d,2p) basis set for all main group elements and the aug-cc-pVTZ-PP pseudo-potential and its associated triple-ζ basis set for Pd and I (BS2 basis set). The solvation free energy corrections were computed at the B3LYP/BS2 level with the IEFPCM model on gas-phase optimized geometries, and 1,4-dioxane was chosen as solvent for consistency with the experiment.

Acknowledgements

The CNRS is gratefully acknowledged for financial support of this research. Our laboratory BioCIS UMR 8076 is a member of the Laboratory of Excellence LERMIT supported by a grant from ANR (ANR-10-LABX-33). We thank the Lebanese University for the award of a research fellowship to J.A. This work was granted access to the HPC resources of CINES under the allocation 2012-086894 made by GENCI (Grand Equipement National de Calcul Intensif).

References

[1] a) E. J. G. Anctil, V. Snieckus, in *Metal-Catalyzed Cross-Coupling Reactions*, Wiley-VCH Verlag GmbH, **2008**, pp. 761-813; b) H. Bönnemann, W. Brijoux, in *Transition Metals for Organic Synthesis*, M. Beller and C. Bolm ed., Wiley-VCH Verlag GmbH, **2008**, pp. 171-197.

[2] V. Michelet, P. Y. Toullec, J.-P. Genêt, *Angew. Chem. Int. Ed.* **2008**, *47*, 4268-4315.

[3] a) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186; b) S. F. Kirsch, *Synthesis* **2008**, *2008*, 3183-3204.

[4] T. Xu, G. Liu, *Org. Lett.* **2012**, *14*, 5416-5419.

[5] a) T. Shibata, Y. Ueno, K. Kanda, *Synlett* **2006**, 0411-0414; b) C. Michon, S. Liu, S. Hiragushi, J. i. Uenishi, M. Uemura, *Synlett* **2008**, 1321-1324; c) J. W. Dankwardt, *Tetrahedron Lett.* **2001**, *42*, 5809-5812; d) M.-Y. Lin, A. Das, R.-S. Liu, *J. Am. Chem. Soc.* **2006**, *128*, 9340-9341.

[6] a) L. Zhang, J. Sun, S. A. Kozmin, *Adv. Synth. Catal.* **2006**, *348*, 2271-2296; b) A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410-3449.

[7] a) G. G. Blond, C. C. Bour, B. B. Salem, J. J. Suffert, *Org. Lett.* **2008**, *10*, 1075-1078; b) N. Chernyak, V. Gevorgyan, *J. Am. Chem. Soc.* **2008**, *130*, 5636-5637; c) T.-J. Meng, Y.-M. Hu, S.-J. Sun, T. Zhu, S. Wang, *Tetrahedron* **2010**, *66*, 8648-8653; d) N. Chernyak, S. I. Gorelsky, V. Gevorgyan, *Angew. Chem. Int. Ed.* **2011**, *50*, 2342-2345; e) J. Petrignet, A. Boudhar, G. Blond, J. Suffert, *Angew. Chem. Int. Ed.* **2011**, *50*, 3285-3289.

[8] a) A. Fürstner, V. Mamane, *J. Org. Chem.* **2002**, *67*, 6264-6267; b) V. Mamane, P. Hannen, A. Fürstner, *Chem. Eur. J.* **2004**, *10*, 4556-4575.

[9] T. Shibata, S. Takayasu, S. Yuzawa, T. Otani, *Org. Lett.* **2012**, *14*, 5106-5109.

[10] a) C. A. Merlic, M. E. Pauly, *J. Am. Chem. Soc.* **1996**, *118*, 11319-11320; b) H.C. Shen, S. Pal, J.-J. Lian, R.-S. Liu, *J. Am. Chem. Soc.* **2003**, *125*, 15762-15763.

[11] a) K. Maeyama, N. Iwasawa, *J. Org. Chem.* **1999**, *64*, 1344-1346; b) T. Miura, N. Iwasawa, *J. Am. Chem. Soc.* **2002**, *124*, 518-519.

[12] For reviews on Gold-catalyzed reactions, see: a) A. Hashmi, K. Stephen, *Chem. Rev.* **2007**, *107*, 3180-3211; b) H. Huang, Y. Zhou, H. Liu, *Beilstein J. Org. Chem.* **2011**, *7*, 897-936; c) E. Jiménez-Núñez, A. M. Echavarren, *Chem. Rev.* **2008**, *108*, 3326-3350.

[13] N. Chernyak, V. Gevorgyan, *Adv. Synth. Catal.* **2009**, *351*, 1101-1114.

[14] For more details on the Au- or Pd-catalyzed cyclization of the enyne **1a**, see the Supporting Informations.

[15] PPh_3AuNTf_2 is a commercial and air stable gold complex, for synthesis of this complex, see: N. Mézailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133-4136.

[16] a) C .V. Ramana, R. Mallik, R. G. Gonnade, *Tetrahedron* **2008**, *64*, 219-233; b) E. Soriano, J. Marco-Contelles, *Organometallics* **2006**, *25*, 4542-4553; c) H. Garcia, S. Iborra, J. Primo, M. A. Miranda, *J. Org. Chem.* **1986**, *51*, 4432-4436; d) T. Hosokawa, S. Yamashita, S.-I. Murahashi, A. Sonoda, *Bulletin Chem. Soc. J.* **1976**, *49*, 3662-3665.

[17] Electronic effects on cycloisomerization reaction play a critical role on the 5-*endo-dig* and 6-*exo-dig* products distribution, see reference 7b.

[18] It was assumed that the geometry of all geometrically pure products was the same as that for **3a** and **3i**, the geometry of which was confirmed by NOESY experiments.

[19] Under Pd-conditions, when enyne 1-((4-methoxyphenyl)ethynyl)-2-(prop-1-en-2-yl)benzene was used, a complete recovery of the starting material was observed. The same result is obtained when we tried the cyclization with 1-(hept-1-yn)-2-(1-phenylvinyl)benzene.

[20] a) N. Krause, C. Winter, *Chem. Rev.* **2011**, *111*, 1994-2009; b) R. Fang, C.-Y. Su, C. Zhao, D. L. Phillips, *Organometallics* **2009**, *28*, 741-748.

[21] Heating an isolated *E*/*Z* mixture of **3a** (*E*/*Z*: 80/20) in dioxane at 150 °C for 5 h furnished **3a** exclusively as a single *E*-isomer.

[22] For more details, see the Supporting Informations.

[23] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara , K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima,

Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr, J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian 09, revision B.01, ed., Gaussian, Inc, , Wallingford, CT., **2010**.

[24] a) C. T. Lee, W. T. Yang, R. G. Parr, *Phys. Rev. B* **1988**, *37*, 785-789; b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648-5652.

[25] a) W. R. Wadt, P. J. Hay, *The Journal of Chemical Physics* **1985**, *82*, 284-298; b) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270-283.

[26] For recent examples, see a) J. Barluenga, L. Florentino, F. Aznar, C. Valdés, *Org. Lett.* **2010**, *13*, 510-513; b) K. V. Tan, J. L. Dutton, B. W. Skelton, D. J. D. Wilson, P. J. Barnard, *Organometallics* **2013**, *32*, 1913-1923; c) P. Roesle, C. J. Dürr, H. M. Möller, L. Cavallo, L. Caporaso, S. Mecking, *J. Am. Chem. Soc.* **2012**, *134*, 17696-17703; d) G. Ali Salman, R. Un Nisa, V. O. Iaroshenko, J. Iqbal, K. Ayub, P. Langer, *Org. Biomol. Chem.* **2012**, *10*, 9464-9473.

[27] Y. Zhao, D. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215-241.

Gold versus Palladium: A Regioselective Cycloisomerization of Aromatic Enynes

Adv. Synth. Catal. **Year**, *Volume*, Page – Page

Jessy Aziz, Gilles Frison, Patrick Le Menez, Jean-Daniel Brion, Abdallah Hamze,* and Mouad Alami*